



THE COMMITTEE ON ENERGY AND COMMERCE

November 12, 2012

MAJORITY MEMORANDUM

TO: Members, Subcommittee on Oversight and Investigations

FROM: Subcommittee on Oversight and Investigations Staff

RE: Hearing on “The Fungal Meningitis Outbreak: Could It Have Been Prevented?”

On Wednesday, November 14, 2012, at 10:00 a.m. in room 2123 of the Rayburn House Office Building, the Subcommittee on Oversight and Investigations will hold a hearing entitled “The Fungal Meningitis Outbreak: Could It Have Been Prevented?”

This hearing will examine the facts surrounding the recent outbreak of fungal meningitis and other infections linked to contaminated injectable products made and distributed by the New England Compounding Center (NECC) in Framingham, Massachusetts. This hearing will also examine the history of complaints associated with NECC and its affiliated entities as well as related inspections and actions taken by the U.S. Food and Drug Administration (FDA) and the Massachusetts Department of Public Health (MDPH).

I. WITNESSES

Panel One

Ms. Joyce Lovelace

Panel Two

Mr. Barry J. Cadden
President, Co-Owner and Director of Pharmacy
New England Compounding Center

Panel Three

The Honorable Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration (FDA)

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Dr. Lauren Smith, MD, MPH
Interim Commissioner
Massachusetts Department of Public Health (MDPH)

II. BACKGROUND – THE CURRENT OUTBREAK

This section of the memorandum details the facts surrounding the current outbreak and the investigation of the outbreak by State and Federal regulators. In Part III, the memorandum describes the history of Federal and State inspections of NECC and resulting regulatory actions since the Massachusetts Board of Registration in Pharmacy (MBP or Massachusetts Board of Pharmacy) approved the company's pharmacy license in 1998.

A. The Fungal Meningitis Outbreak

As of November 9, 2012, the Centers for Disease Control and Prevention (CDC) has confirmed that 32 people have died and 438 people have been sickened across 19 states after receiving contaminated injectable products made and distributed by NECC.

The first case of meningitis connected to this outbreak was confirmed on September 18, 2012, in Tennessee. On September 21, 2012, CDC was notified by the Tennessee Department of Health (TDH) of a patient with the onset of meningitis approximately 19 days after receiving an epidural steroid injection at an ambulatory surgical center in Nashville. By September 24, 2012, TDH officials contacted MDPH informing them that it was investigating an outbreak of fungal meningitis in six patients at the same Nashville facility, with onsets between July 30 and September 18, 2012. All six patients had received the same injectable steroid, preservative-free methylprednisolone acetate (80 mg/ml), compounded and distributed by NECC.

On September 25, 2012, CDC informed FDA of the situation and that three lots of methylprednisolone acetate were suspected. Methylprednisolone acetate is a type of injectable steroid suspension often used to treat pain and swelling. MDPH convened a multi-agency teleconference with CDC, FDA, and Tennessee officials. Mr. Barry Cadden and Mr. Gregory Conigliaro, principal owners of NECC, joined the call as well. Mr. Cadden and Mr. Conigliaro immediately provided documentation of all facilities that had received shipments from the three suspect lots of methylprednisolone acetate. On September 26, 2012, NECC instituted a voluntary recall of the suspect lots. In total, 17,676 doses had been shipped to customers in 23 states. More than 14,000 patients had already received a potentially contaminated injection. Based on surveillance efforts, CDC soon identified a patient in North Carolina displaying symptoms of meningitis after receiving an injection from one of the suspect lots.

From September 26, 2012, through October 5, 2012, investigators from FDA's New England District Office (FDA NWE-DO) and MDPH inspected the NECC facility. During their inspection, State and Federal investigators observed visible black particulate matter in sealed vials of purportedly sterile methylprednisolone acetate that had been returned to NECC. MDPH noted that NECC's records showed inconsistencies in sterilization processes. The Massachusetts Board of Pharmacy voted to obtain a voluntary surrender of NECC's license, which NECC

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agreed to on October 3. NECC also agreed to a voluntary recall of all products intended for injection into the area around the spinal cord or brain. On October 4, FDA and MDPH confirmed that fungal contamination had been identified in a vial from one of the suspect lots. FDA and CDC recommended that all health care professionals cease use and remove any material produced by NECC from their facilities.¹ On October 6, NECC announced a voluntary recall of all NECC products currently in circulation. On October 8, Mr. Cadden and Mr. Glenn Chin² voluntarily ceased practice as pharmacists pending completion of the investigation.³ In addition to the evidence of contamination, investigators also found evidence that the NECC had not been compounding drugs for patient-specific prescriptions. Instead, the NECC accepted patient lists generated by a clinical facility and provided to NECC for the purpose of obtaining its products. On October 16, agents from FDA's Office of Criminal Investigations, along with local authorities, raided the NECC Framingham, Massachusetts facility.

The MDPH and FDA also inspected two other companies owned by Barry Cadden, Ameridose, LLC (Ameridose) and Alaunus Pharmaceutical, LLC (Alaunus) on October 10, 2012, and October 14, 2012, respectively. NECC, Ameridose, and Alaunus share common ownership and corporate structures. Cadden is a co-owner of Ameridose, a pharmacy and wholesaler based in Westborough, Massachusetts, and Alaunus, a wholesaler located next to NECC in Framingham. Cadden, his wife, Lisa Conigliaro-Cadden, her brother, Gregory Conigliaro, and his wife, Carla Conigliaro, serve as directors of all three companies. Based on their shared ownership, MDPH requested that Ameridose and Alaunus cease all pharmacy operations and the manufacturing and distribution of any products. According to MDPH, Mr. Cadden agreed to immediately resign as manager, director and from any other management position at NECC, Ameridose, and Alaunus.

The FDA's investigation of the fungal meningitis outbreak has expanded beyond NECC's methylprednisolone acetate product. For example, FDA confirmed the report of a patient with meningitis-like symptoms potentially caused by epidural injection of a different NECC product, triamcinolone acetonide. In addition, one transplant patient developed a fungal infection after having been administered NECC-produced cardioplegic solution during surgery. Based on these reports, FDA announced that the sterility of any injectable drugs, including ophthalmic drugs that are injectable or used in conjunction with eye surgery, and cardioplegic solutions produced by NECC are of significant concern. FDA recommended that patients who received these products on or after May 21, 2012, be alerted to the potential risk of infection.

¹ FDA subsequently released definitive laboratory confirmation of the presence of fungal contaminants in sealed vials of methylprednisolone acetate in two of the three suspected lots from NECC. As of November 3, 2012, testing of the third lot, as well as other NECC products, was ongoing.

² MDPH referred to Mr. Chin as a "leader[] at NECC" in its preliminary investigative report. MASS. DEP'T OF PUB. HEALTH, NEW ENGLAND COMPOUNDING CENTER (NECC) PRELIMINARY INVESTIGATION FINDINGS: BD. OF REGISTRATION IN PHARMACY REPORT, at 7 (Oct. 23, 2012) [hereinafter, "MDPH OCT. 23, 2012 REPORT"]. In a discussion with Committee staff, Mr. Chin's counsel stated that he started with the company on April 21, 2004 and was the compounding pharmacist in one of NECC's clean rooms until the company ceased operations.

³ On October 22, 2012, MBP authorized MDPH staff to request voluntary permanent surrender of the licenses of Barry Cadden, Glenn Chin, and Lisa Conigliaro-Cadden, as well as NECC. According to MDPH, in response to an inquiry from Committee staff on November 4, this process is ongoing.

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FDA reported on October 31, 2012, that Ameridose was voluntarily recalling all of its unexpired products in circulation. While the investigation remained open at the time of the announcement, FDA stated that its preliminary findings raised sterility concerns. The agency further clarified that the recall was not based on reports of patients with infections associated with any Ameridose product.

On November 1, 2012, FDA and CDC released laboratory results that confirmed contaminants in two other NECC products: preservative-free betamethasone repository injection and cardioplegia solution. Bacteria were present in three separate lots of betamethasone and in a single lot of cardioplegia solution. CDC continues to investigate reports of potential infections in patients receiving NECC products. As of November 1, CDC had not received reports of laboratory-confirmed cases of infection due to bacteria present in betamethasone or cardioplegia solution from NECC.

B. Preliminary Findings Released by State and Federal Regulators Regarding the Outbreak

On October 23, 2012, MDPH issued a Board of Registration in Pharmacy Report setting forth its preliminary findings relating to the ongoing investigation into the outbreak.⁴ In addition, on October 26, 2012, FDA released its inspectional observations as well as a corresponding Form FDA 483 (483) to NECC.⁵

As previously discussed, investigators from FDA NWE-DO and MDPH first visited the NECC facility in connection with this outbreak on September 26, 2012. According to MDPH, upon arriving at NECC, investigators found NECC employees cleaning sterile compounding areas. They also detected signs of bleach decontamination.⁶ Despite NECC's apparent attempt to present the facility as compliant, State investigators still identified "serious deficiencies and significant violations of pharmacy law and regulations that clearly placed the public's health and safety at risk."⁷

During the facility inspections, MDPH documented numerous deficiencies and violations, including the following:

⁴ See MDPH OCT. 23, 2012 REPORT, *supra* note 2. MDPH noted that this report constitutes early findings that may be subject to revision as the investigation unfolds. *Id.* at 2.

⁵ See U.S. FOOD & DRUG ADMIN., NEW ENGLAND COMPOUNDING CENTER FORM FDA 483 (Oct. 26, 2012), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/UCM325980.pdf> [hereinafter, "FDA OCT. 26, 2012 FORM 483"]. FDA issues a Form 483 at the end of an inspection when the investigators believe that the observed conditions or practices, in their judgment, may indicate violations of the Food, Drug, and Cosmetic Act or any related regulations. FDA has stated that its goal in issuing a 483 is to have the company act quickly to correct potential violations. The FDA considers the 483 along with an Establishment Inspection Report (EIR), prepared by FDA investigators, and any other information, including any responses received from the company. The agency then considers whether further action is appropriate.

⁶ MDPH OCT. 23, 2012 REPORT, *supra* note 2, at 6.

⁷ *Id.* at 2.

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- NECC distributed large batches of compounded sterile products directly to facilities for apparent general use rather than requiring a prescription for an individual patient.⁸
- NECC distributed two of the recalled lots of methylprednisolone acetate prior to receiving results of sterility testing.⁹
- Final sterilization of product did not follow proper standards pursuant to United States Pharmacopeia Standard 797 (USP 797) and NECC's own Standard Operating Procedures.¹⁰
- NECC failed to test its autoclaves to ensure proper function.¹¹
- Visible black particulate matter was seen in several recalled sealed vials of methylprednisolone acetate.¹²
- "Tacky" mats located outside the clean room were visibly soiled with assorted debris, violating USP 797.¹³
- A leaking boiler adjacent to the clean room had created a pool of water, an environment susceptible to contaminant growth.¹⁴

FDA investigators documented similar observations in the 483, as well as additional problems with NECC's ability to maintain its clean room and ensure the sterility of its products, as further supported by sample testing results. FDA's observations included the following:

- Eighty-three vials out of a bin containing 321 vials of methylprednisolone acetate from one of the suspect lots contained what appeared to be greenish black foreign matter. Seventeen vials from the same bin were observed to contain what appeared to be white filamentous material. Fifty of these vials were sent to an FDA laboratory for testing and all 50 tested positive for microbial contamination.¹⁵

⁸ *Id.* at 3.

⁹ *Id.* at 4. MDPH noted that while NECC's records showed that the sterility tests found no contamination, the adequacy of NECC's sterility testing methods remained under examination.

¹⁰ *Id.*

¹¹ *Id.* An autoclave is a device used to sterilize equipment by subjecting it to high pressure steam. If done properly, all bacteria and fungi would be inactivated.

¹² *Id.*

¹³ *Id.* A clean room is an enclosed space that is designed and maintained to have a controlled environment with low levels of airborne particles and surface contamination. Production of sterile drug products in a properly functioning and maintained clean room reduces the risk of the introduction of microbial contamination into the drug during processing, including filling into its final container.

¹⁴ *Id.* at 5.

¹⁵ FDA OCT. 26, 2012 FORM 483, *supra* note 5, at 1.

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- NECC provided no documentation or evidence to support that the autoclave used to sterilize suspensions formulated using non-sterile active pharmaceutical ingredients and raw materials was effective.¹⁶
- NECC is abutted to the rear by a recycling facility producing airborne particulates. NECC rooftop HVAC units were estimated to be located approximately 100 feet from the recycling facility.¹⁷
- NECC's air conditioning was turned off at night, including in the clean rooms, despite the importance of maintaining a consistent temperature and level of humidity.¹⁸
- NECC's own environmental monitoring program yielded violative levels of bacteria and mold in clean rooms used for the production of sterile drug products, between January 2012 and September 2012. Despite the company's action limits having been exceeded, there was no investigation conducted by the company, no identification of the isolates, no product impact assessments conducted, and no documented corrective actions taken to remove the microbial contamination from the facility.¹⁹

Further, according to Steven Lynn, Director of FDA's Office of Manufacturing and Product Quality, on an October 26, 2012, media call describing FDA's observations and test results, there was overgrowth of bacteria or fungi in at least one sample testing dish. When asked to clarify what he meant, Mr. Lynn stated, "Think of a plant just growing out of control."²⁰

III. HISTORY OF STATE AND FEDERAL INVESTIGATIONS OF NECC

While investigating the meningitis outbreak over the last six weeks, FDA and MDPH investigators have observed many serious deficiencies and significant violations of law and good compounding practices. These violations, however, were not a first for NECC. Documents produced to the Committee by the FDA and the Massachusetts Board show that NECC has a long history of very similar, if not identical, underlying misconduct. Some of the violations observed by regulators as early as 2002 include the company's failure to maintain adequate safeguards for sterile injectable products – the very issue at the center of the current meningitis outbreak. In fact, since the company's formation, FDA conducted three prior series of inspections of NECC, each based on a separate set of allegations or events, issuing two Form 483s in 2002 and 2003 and one Warning Letter in 2006. The Massachusetts Board of Pharmacy has an even more extensive history with NECC. Prior to this outbreak, the Board had investigated at least twelve separate complaints concerning NECC or Mr. Cadden, issued at least

¹⁶ *Id.*

¹⁷ *Id.* at 7.

¹⁸ *Id.* at 1.

¹⁹ *Id.*

²⁰ Media Call, U.S. Food & Drug Admin., FDA Media Call: Fungal Meningitis Outbreak – FDA Inspection Observations (Form 483) at NECC (Oct. 26, 2012) (statement of Steven Lynn, Dir., Office of Mfg. & Product Quality, Office of Compliance, Ctr. for Drug Evaluation & Research, FDA).

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four advisory letters and/or informal reprimands, and entered into a consent agreement with the company in 2006.

Set forth below is the chronology of FDA's and the Massachusetts Board's inspections and involvement with the NECC, including any resulting administrative actions.

A. Formation of NECC

On May 12, 1998, MBP approved NECC's pharmacy license. Mr. Barry Cadden was listed as the managing pharmacist. Less than a year later, in April 1999, MBP filed a complaint against Mr. Cadden for providing a practitioner with blank prescription pads referring to NECC, in clear violation of MBP regulations.²¹ The MBP Complaint Committee reviewed the complaint on October 19, 1999, and voted to issue an informal reprimand to Mr. Cadden and NECC and dismiss the case.

NECC's efforts to market its products were the subject of additional complaints starting in 2001. On June 27, 2001, MBP staff completed an investigation into a report submitted by the Idaho Board of Pharmacy that NECC was soliciting business for drug products which should have been discontinued by the manufacturer. In addition, on April 18, 2002, MBP received a letter from the Nevada Board of Pharmacy describing allegations of NECC selling non FDA-approved products to physicians in Nevada. Committee staff is unaware of any additional administrative or disciplinary actions taken as a result of these reports.

Further, based on various complaints of unprofessional conduct and failure to adhere to standards of practice between 2002 and 2004, MBP issued three advisory letters to Mr. Cadden and NECC on September 30, 2004. Each of the advisory letters addressed complaints made by out-of-state pharmacists or practitioners in Texas, South Dakota, Iowa, and Wisconsin. Each of these complaints related to NECC's solicitation of out-of-state prescriptions for office use. The three advisory letters issued by the Massachusetts Board stated that the letters did not constitute disciplinary action but communicated the Board's concern regarding the conduct that was the basis for the complaint. The letters requested that NECC adopt "quality assurance measures . . . to reduce the risk of recurrence."²²

B. 2002 Inspections Related to Betamethasone Repository Injection

In March 2002, two adverse events were reported to FDA through its MedWatch system.²³ Both adverse events involved epidural betamethasone repository injections

²¹ 247 CMR § 9.01(1),(13).

²² Advisory Letter from James T. Devita, President, Mass. Bd. of Registration in Pharmacy, to Barry Cadden, Manager of Record, New England Compounding Ctr. (Sept. 30, 2004) (Docket Nos. DS-03-060, PH-03-070 – Texas). *See also* Advisory Letter from James T. Devita, President, Mass. Bd. of Registration in Pharmacy, to Barry Cadden, Manager of Record, New England Compounding Ctr. (Sept. 30, 2004) (Docket Nos. DS-04-062, PH-04-161 – Iowa and Wisconsin) *and* Advisory Letter from James T. Devita, President, Mass. Bd. of Registration in Pharmacy, to Barry Cadden, Manager of Record, New England Compounding Ctr. (Sept. 30, 2004) (Docket Nos. DS-03-036, PH-03-042 – South Dakota).

²³ The investigative report corresponding to an April 16, 2002 FDA Form 483 states that FDA investigators contacted the MedWatch reporter who informed them that "a total of probably 5 incidents occurred after using

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(betamethasone acetate and betamethasone sodium phosphate suspension 6 mg/ml), from the same lot compounded and distributed by NECC. Like methylprednisolone acetate, betamethasone repository injections are steroid solutions often used to treat pain and swelling. FDA alerted the MBP and invited them to participate in an inspection commencing April 9, 2002. FDA noted in its investigative report that the agency had no previous investigation or inspection history with the firm, though MBP had inspected NECC in the past.

While the investigation was underway, FDA investigators were informed of the fact that this was the same formulation compounded by a pharmacy in California that was associated with numerous hospitalizations (including five cases of meningitis, three of which were fatal) in Walnut Creek, California the previous year. Before detailing areas of concern and related discussions with NECC management, FDA's investigative report states, "Very similar operational problems existed with the California Compounding Pharmacy that were encountered with NEC[C]." ²⁴

On the day the inspection began, Barry Cadden was identified as the Owner and Director of Pharmacy at NECC. He identified his wife, Lisa Cadden, as Vice President and introduced her to investigators on the second day of the inspection. According to the report, Mr. Cadden stated that NECC had eight employees, three of whom were involved in compounding, though he was the only individual who compounded sterile product. He informed investigators that "they fill patient specific prescriptions only, and that they have no wholesale functions." ²⁵

According to FDA's inspection report, on the first day of the inspection, "Mr. Cadden was cooperative [and] supplied some documents. The second day of the inspection, Mr. Cadden had a complete change in attitude [and] basically would not provide any additional information either by responding to questions or providing records. Mr. Cadden challenged FDA jurisdiction/authority to be at his pharmacy." ²⁶ FDA investigators were initially "allowed to review and were furnished with copies of records related to the compounding of Betamethasone Repository Injection," though by the second day, "Mr. Cadden stated that he was no longer willing to provide us with any additional records, unless we would identify the specific lot . . .

subject Betamethasone on patients." U.S. FOOD & DRUG ADMIN., FDA INSPECTION REPORT OF NEW ENGLAND COMPOUNDING PHARMACY, INC., at 4 (Apr. 16, 2002) [hereinafter, "FDA APR. 16, 2002 INSPECTION REPORT"]. In a February 2003 presentation to MBP, FDA identified the adverse events as "dizziness, shortness of breath, diaphoresis, drop in blood pressure to 55/44." U.S. Food & Drug Admin., *Inspectional History of New England Compounding Center (NECC)*, Presentation to Bd. of Registration in Pharmacy, Div. of Health Professions Licensure, Dep't of Pub. Health, Commonwealth of Mass. (Feb. 5, 2003) [hereinafter, "Feb. 5, 2003 FDA Presentation"].

²⁴ FDA APR. 16, 2002 INSPECTION REPORT, *supra* note 23, at 3.

²⁵ *Id.* at 6.

²⁶ *Id.* at 2. Questions and discussion regarding issues related to FDA's jurisdiction and authority are addressed in detail later in this memorandum. With respect to the April 2002 inspection, the FDA investigative report cites § 704(a) of the FDCA, which describes the nature of FDA inspectional authority with regard to drug manufacturers, pharmacies, and other entities, and specifically excludes traditional retail pharmacies, operating in accordance with local pharmacy laws, from being obligated to furnish certain records. The report summarizes, that the investigators' inspectional authority at pharmacies operating in a retail capacity consists of being able to "enter, at reasonable times (Section 704(a)(1)(A), and inspect, at reasonable times, and within reasonable limits and in a reasonable manner (Section 704(a)(1)(b), the establishment and its equipment and operations. However, the owner of the pharmacy is not obligated to furnish records, as is normally the case when a facility that processes drug products is being inspected." *Id.*

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that was the focus of this investigation. Since we had been specifically directed by [FDA's Office of Compliance in the Center for Drug Evaluation and Research (CDER)] not to divulge this lot number, we were not in a position to comply with Mr. Cadden's request. From this point on, no additional records were provided or collected."²⁷

Nonetheless, FDA investigators had managed to obtain a printout of the betamethasone products compounded by NECC in 2002 and identified the suspect lot on the list, which according to the lot number was compounded on February 1, 2002. Mr. Cadden informed FDA that there were no compounding records associated with the suspect lot number. According to FDA's report, Mr. Cadden stated that he did not believe betamethasone was ever compounded for that lot number, although FDA noted that Mr. Cadden "could not provide any documents to support his belief, such as a cancelled lot etc."²⁸ Further, FDA investigators contacted the healthcare professional who reported the adverse events to confirm that the suspect lot existed. That individual informed FDA that he had returned the betamethasone product to NECC and, in fact, had spoken by telephone to Mr. Cadden about the incident.²⁹

While FDA's investigative report did not mention any test results of the suspect lot in question, the MBP report stated, "The FDA was concerned regarding a specific date the Batch of Betamethasone Repository 6mg/ml was compounded. The error was first reported in March 2002. The unnamed facility conducted sterility and Endotoxin tests on the product prepared by NECC, the results indicated a positive test for Endotoxin."³⁰ While FDA did not include this specific test result in its investigative report, FDA did discuss other positive endotoxin test results of betamethasone samples from NECC lots.

According to the FDA report, on April 9, 2002, "Mr. Cadden stated on/about 3/19/02 through 4/6/02 he received ARL [(Analytical Research Laboratories)] results positive for endotoxin (greater than 100 ppb). . . . He stated these lots (about 4 lots total) were awaiting disposal at his facility."³¹ After changing the suspending agent based on research he conducted, Mr. Cadden informed investigators that he made an additional lot on April 6, 2002. He stated that he "sent his samples to ARL, then left the product beaker covered with aluminum foil on the magnetic stirrer in the hood awaiting lab results" and that it "could take anywhere from seven to ten days to obtain lab results."³² When questioned about this practice, "Mr. Cadden stated he didn't want to waste the money on vials or the effort in transfilling the vials if the 4/6/02 lot failed testing. He stated he would transfill the vials upon receiving satisfactory lab results."³³ FDA investigators "discussed with Mr. Cadden that this was not an acceptable process for maintaining product sterility."³⁴ When FDA investigators returned to NECC on April 10, "the

²⁷ *Id.* at 3.

²⁸ *Id.* at 4.

²⁹ *Id.*

³⁰ MASS. DEP'T OF PUB. HEALTH, INVESTIGATION REPORT OF NEW ENGLAND COMPOUNDING CENTER & BARRY CADDEN, at 5 (Mar. 4, 2004) [hereinafter, "MDPH MAR. 4, 2004 INVESTIGATION REPORT"].

³¹ FDA APR. 16, 2002 INSPECTION REPORT, *supra* note 23, at 7. Analytical Research Laboratories (ARL) is a third-party analytical testing lab located in Oklahoma City, Oklahoma that NECC has sent samples to for sterility and endotoxin testing since at least 2002.

³² *Id.*

³³ *Id.*

³⁴ *Id.*

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hood was clean and Mr. Cadden was asked the whereabouts of the 4/06/02 lot. He stated he received negative lab results the night before, and had transfilled the lot into vials that morning. He accredited the positive endotoxins to the previous suspending agent.”³⁵ FDA did not comment on this assertion, nor is it known how long Mr. Cadden had been using the previous suspending agent. According to the report, “The FDA investigator suggested to Mr. Cadden that he retest the 4/6/02 lot again after transfilling the vials since the product sat in a beaker for 5 days,” which he agreed to do.³⁶

After completing the inspection, FDA investigators concluded that “[d]ue to jurisdiction/confidentiality restrictions, this FDA investigation could not proceed to any definitive resolution of issues raised in the [FDA] Headquarters assignment” and that individuals in CDER’s Office of Compliance “were fully informed of problems/barriers that were encountered throughout the inspection.”³⁷ FDA’s investigative report was finalized on April 16, 2002. Prior to concluding the investigation, FDA investigators spoke with officials in CDER’s Office of Compliance and FDA NWE-DO about NECC’s “poor practices and areas of concern” and “impressed upon [them] that due to limitations on information gathering and access to records, the FD-483 observations could not/would not be supported with documentation.”³⁸ Nonetheless, “FDA Investigators were directed to issue the 483 (even in light of the lack of documentation).”³⁹ The observations in the 483 focused primarily on two violations: the sterility of the betamethasone product and NECC’s failure to account for records related to the suspect lot of betamethasone, which subsequently tested positive for endotoxin.⁴⁰

After issuing the 483, Mr. Cadden was given an opportunity to respond to FDA investigators’ observations during an exit interview. With regard to the sterility of the beaker, and keeping the solution in the beaker for seven to ten days while waiting for test results, Mr. Cadden claimed that this was not his usual practice.⁴¹ FDA’s report also indicated that Mr. Cadden provided contradictory information to the agency. During the exit interview, Mr. Cadden claimed that the beaker capped with foil “didn’t contain the betamethasone repository.”⁴²

The report completed by the Massachusetts Board substantiated FDA’s observations about NECC’s practices. Specifically, it noted that the beaker remained in the hood capped with foil while tests were conducted, a process which could take up to seven days.⁴³

In February 2003, following the April 2002 inspections with FDA, the MBP filed formal complaints against NECC and Mr. Cadden “based on the failure to adhere to standards of practice for compounding prescriptions. Specifically, the pharmacy and pharmacist engaged in unprofessional conduct as exhibited by[:] failing to follow guidelines, sterility procedures, record

³⁵ *Id.*

³⁶ *Id.*

³⁷ *Id.* at 5.

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ See U.S. FOOD & DRUG ADMIN., NEW ENGLAND COMPOUNDING PHARMACY, INC. FORM FDA 483 (Apr. 16, 2002) [hereinafter, “FDA APR. 16, 2002 FORM 483”].

⁴¹ See FDA APR. 16, 2002 INSPECTION REPORT, *supra* note 23, at 10.

⁴² *Id.*

⁴³ See MDPH MAR. 4, 2004 INVESTIGATION REPORT, *supra* note 30, at 6.

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keeping requirements, [and] batch records [requirements], [and] failing to provide certificates of analysis, proof of sterility testing, Endotoxin test results, batch numbers and prescriptions upon request.”⁴⁴

On February 7, 2003, the MBP investigator requested that NECC provide responses to certain questions raised during the investigation. Documents produced to the Committee show that the Massachusetts Board found that NECC took certain corrective measures in February 2003, including hiring a consultant to develop policy and procedures.⁴⁵ The MBP subsequently conducted follow-up inspections on February 20, 2003, and one year later on February 20, 2004. According to the MBP report, the investigator found the facility was in compliance.⁴⁶ Even so, the MBP investigator recommended that the Board issue a formal reprimand to NECC. According to the report, which was signed by the investigator and her supervisor on March 4, 2004, the investigator based her decision on NECC’s “history as it relate[d] to prior concerns of the Board agents since 1999[.]”⁴⁷

One particular concern, which was raised between the investigator’s April 2002 inspections with FDA and her recommendation for formal reprimand, may have informed her decision. In October 2002, FDA investigators informed the MBP that a second incident with NECC had occurred, this one involving methylprednisolone acetate.⁴⁸

C. 2002 Inspections Related to Methylprednisolone Acetate

On October 2, 2002, CDER’s Office of Compliance requested an FDA NWE-DO investigation to obtain information regarding three MedWatch reports associated with the use of methylprednisolone acetate that was compounded by NECC in May 2002. According to FDA’s investigative report, the three MedWatch reports were reported by a physician and the chief pharmacist at a hospital in Rochester, New York and detailed adverse events that occurred in two patients on July 17, 2002, after they had received intrathecal injections. After speaking with hospital staff, FDA documented that both patients were hospitalized with meningitis-like symptoms, received antibiotics, and fully recovered. Hospital staff reported that the vials from the same lot distributed by NECC were tested at the hospital and confirmed positive for bacteria. When asked about actions taken by the hospital, the hospital’s chief pharmacist stated that he “instructed his staff to remove all the methylprednisolone acetate injectable with the affected lot number from the hospital floors.”⁴⁹ The hospital’s quality assurance supervisor stated that she first contacted Mr. Cadden on or about July 23, 2002, “to make him aware of the adverse events.”⁵⁰ She informed the FDA investigator that “she does not believe [the hospital] returned any of the vials to NECC” and that “[s]he believes they were all retained for FDA sampling and hospital investigative purpose.”⁵¹

⁴⁴ *Id.* at 4.

⁴⁵ *Id.* at 6.

⁴⁶ *See id.* at Attachment 1.

⁴⁷ *Id.* at 9.

⁴⁸ *Id.* at 7.

⁴⁹ U.S. FOOD & DRUG ADMIN., FDA INSPECTION REPORT OF NEW ENGLAND COMPOUNDING CENTER, at 4 (Feb. 10, 2003) [hereinafter, “FDA FEB. 10, 2003 INSPECTION REPORT”].

⁵⁰ *Id.* at 5.

⁵¹ *Id.*

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On September 9, 2002, FDA's New York District Office collected a sample from the hospital, purportedly from the suspect lot. The sample was then sent to FDA's Northeast Regional Lab (NRL) for sterility and endotoxin testing. However, according to FDA's report, NRL "was unable to perform the sample analysis until 4 days after the compounded product's expiration date" and the sample collected from the hospital was from "a different lot than the MedWatch reports."⁵²

FDA and MBP investigators first visited NECC in relation to the adverse events associated with methylprednisolone acetate on October 24, 2002. FDA's investigation report noted that FDA last inspected NECC in April 2002 and a 483 was issued to Mr. Cadden citing "sterility issues pertaining to the transfilling practices for betamethasone repository injection."⁵³ The report further stated that "[t]he practices that were cited on the previous FDA 483 were not in place and therefore the correction of these items was not an issue" during the current inspection.⁵⁴ The report also highlighted the fact that since April 2002, NECC's operating space approximately doubled in size and it was now "planning on marketing and selling compounded products in all 50 U.S. states per Mr. Cadden."⁵⁵

Mr. Cadden informed the FDA inspector that he had been "telephoned by an employee from [the Rochester hospital] to notify him of the adverse reactions" and that the employee "told him the adverse reactions were due to 'administration errors' since the injections were administered intrathecally."⁵⁶ According to FDA's investigator, Mr. Cadden stated that the hospital had in fact "returned vials of the affected product to the firm and that NECC sent a sample of the returned product to its contract laboratory [ARL] for testing."⁵⁷ The test results, which were reported to the FDA investigator on August 22, 2002, came back negative for endotoxin content and microbial contamination.

On December 11, 2002, FDA NRL informed FDA NWE-DO that four out of fourteen of the vials it sampled from the lot provided by the New York District Office tested positive for bacteria. On December 12, FDA and MBP investigations returned to NECC with the test results to "determine what his intentions would be regarding the compounded product."⁵⁸ Mr. Cadden informed them that "NECC had conducted a recall of the product in August 2002,"⁵⁹ a fact that he failed to share with the investigators during the October 24 inspection. When asked about details of the recall, Mr. Cadden stated that he had "received 500-600 vials back from customers as a result of the recall. He retested one (1) of these vials for sterility and endotoxin and the results were negative."⁶⁰ The inspectors were understandably concerned that this was not a

⁵² *Id.*

⁵³ *Id.* at 3.

⁵⁴ *Id.* at 1.

⁵⁵ *Id.* at 3.

⁵⁶ *Id.* at 7.

⁵⁷ *Id.*

⁵⁸ *Id.* at 8.

⁵⁹ *Id.*

⁶⁰ *Id.*

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representative sample and explained to Mr. Cadden that “the USP contains guidance on sample sizes in relation to lot quantities.”⁶¹

While at the firm on December 12 and again on December 18, 2002, inspectors collected samples of methylprednisolone acetate as well as betamethasone repository injection. According to FDA’s report, “[t]hese compounds were chosen because they were associated with the current and April 2002 MedWatch reports” and are “compounded by similar methods according to Mr. Cadden.”⁶² One FDA investigator returned to NECC on January 14 and 15, 2003. Mr. Cadden notified him that “if [he] had any other requests or questions pertaining to any of their procedures and compounding activities, [he] was to put [his] requests or questions in writing.”⁶³ According to the investigator, Mr. Cadden brought this up when the investigator “requested the address and name of customers who received [the suspect lot of] methylprednisolone . . . [acetate] injection. . . .”⁶⁴ The investigator followed up after the inspection with a written request for the names and customers. Neither Mr. Cadden nor his lawyer chose to respond to the written request and still had not done so when, weeks later on February 10, 2003, the FDA issued NECC a 483 that detailed concerns observed during the inspections.⁶⁵

On February 5, 2003, prior to FDA’s issuance of the Form 483 to NECC, a meeting was convened with officials from FDA NWE-DO, CDER’s Office of Compliance, and MBP in order to “review the inspectional history of the New England Compounding Center and develop a joint strategy for achieving safe compounding practices at the firm.”⁶⁶ The immediate concern was determining how to ensure the outstanding violative betamethasone was removed from commerce. Asserting its authority under section 501(b) of the FDCA, FDA discussed its ability to seize the adulterated lot that “is still within expiry.”⁶⁷ While NECC did ultimately agree to a voluntary recall, officials also discussed alternative courses of action they should consider. CDER officials “reminded everyone that in a similar situation with a South Carolina compounding pharmacy, FDA issued a press release when the firm failed to take recall action in a timely manner.”⁶⁸ Based on a PowerPoint slide deck attached to an FDA memorandum describing the February 5, 2003, meeting, it is clear that FDA was discussing a fungal meningitis outbreak that had occurred a few months prior in South Carolina associated with methylprednisolone acetate compounded by a facility in Spartanburg, South Carolina, which ultimately resulted in two deaths.⁶⁹

⁶¹ *Id.* Mr. Cadden informed investigators on December 18, 2002, in a related discussion about sample sizes, that he “used the recommendations of his contract laboratory (ARL).” *Id.* at 9.

⁶² *Id.* at 8.

⁶³ *Id.* at 11.

⁶⁴ *Id.*

⁶⁵ *See id.*

⁶⁶ Memorandum from Kristina Joyce, Consumer Safety Officer, New England Dist. Office, FDA & Mark Lookabaugh, Compliance Officer, New England Dist. Office, FDA, to Central File, *February 5, 2003 Meeting with Massachusetts Board of Pharmacy/Division of Professional Licensure (239 Causeway Street, Boston, MA 02114)*, at 1 (Feb. 24, 2003) [hereinafter, “Feb. 24, 2003 FDA Memorandum”].

⁶⁷ *Id.* at 2.

⁶⁸ *Id.*

⁶⁹ *See* Feb. 5, 2003 FDA Presentation, *supra* note 23, at 7-8. *See also* David Brown, *Previous Fungal Meningitis Outbreak a Decade Ago Resulted in No Oversight Changes*, WASH. POST (Nov. 5, 2012), http://www.washingtonpost.com/national/health-science/previous-fungal-meningitis-outbreak-a-decade-ago-resulted-in-no-oversight-changes/2012/11/05/8417d84e-1fa8-11e2-9cd5-b55c38388962_story.html.

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At this point, “[a] discussion was held to decide if NECC should be considered a manufacturer or a compounder,” which would govern how to handle the betamethasone recall, but also inform ways to address “NECC’s poor compounding practices [that] would not necessarily be ultimately resolved by such an action.”⁷⁰ It was decided that “current findings supported a compounding role” and that “the state would be in a better position to gain compliance or take regulatory action against NECC as necessary.”⁷¹ It is noteworthy that after closing out the inspection report by issuing the 483 and convening this meeting with State officials, FDA’s primary NECC investigator and her supervisor recommended that the “firm be prohibited from manufacturing until they can demonstrate ability to make product reproducibly and dependably.”⁷² They further noted that if the State was “unwilling to take action, [they] recommend[ed the] firm be enjoined for GMP deficiencies.”⁷³

With respect to next steps, it was agreed that the State would ask Mr. Cadden “to appear before the Board of Pharmacy to answer to the current complaints.”⁷⁴ MBP counsel Susan Manning discussed the fact that “Massachusetts pharmacy law states that pharmacists must act in accordance with USP recommendations” and that “this alone would imply he could be held to those standards by the state.”⁷⁵ In addition, she stated that “although the state’s authority does not include the ability to fine pharmacists, the state is able to take actions against a pharmacy’s license, including revocation and suspension.”⁷⁶ It was agreed that CDER’s Office of Compliance “would work on documenting the deviations from USP standards for the state.”⁷⁷ Furthermore, among other things, the State requested from FDA examples of previous consent agreements and MedWatch reports regarding adverse events from products compounded by NECC.⁷⁸

The February 5, 2003, meeting concluded by FDA “emphasizing the potential for serious public health consequences if NECC’s compounding practices, in particular those relating to sterile products, are not improved.”⁷⁹ FDA acknowledged that “so long as a pharmacy’s operations fall within the scope of the practice of pharmacy (as outlined in FDA’s Compliance Policy Guide 460.200), FDA will generally continue to defer to state authorities for regulatory oversight. In such cases FDA will seek to engage cooperative efforts aimed at achieving regulatory compliance and ensuring the safety and quality of compounded products.”⁸⁰

On February 10, 2003, FDA issued a Form 483 to NECC and met with Mr. Cadden to review the documented observations, which included inadequate documentation to verify whether sterile drug products met set standards, a failure to maintain complaint files, and a lack

⁷⁰ Feb. 24, 2003 FDA Memorandum, *supra* note 66, at 2.

⁷¹ *Id.*

⁷² U.S. FOOD & DRUG ADMIN., FDA ESTABLISHMENT INSPECTION REPORT OF NEW ENGLAND COMPOUNDING CENTER, at 1 (Feb. 10, 2003) [hereinafter, “FDA FEB. 10, 2003 ESTABLISHMENT INSPECTION REPORT”].

⁷³ *Id.*

⁷⁴ Feb. 24, 2003 FDA Memorandum, *supra* note 66, at 3.

⁷⁵ *Id.*

⁷⁶ *Id.*

⁷⁷ *Id.*

⁷⁸ *See id.*

⁷⁹ *Id.*

⁸⁰ *Id.* at 3-4.

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of documentation for the reported adverse events associated with the suspect lot of methylprednisolone acetate.⁸¹ In addition, FDA noted in the corresponding inspection report that results from the samples investigators collected from NECC “revealed that the firm has sterility and potency issues with injectable steroid suspensions (betamethasone repository USP and methylprednisolone acetate USP).”⁸² During the meeting, Mr. Cadden was informed that “at this point the FDA is considering NECC a pharmacy compounding and not a drug manufacturer.”⁸³

On February 26, 2003, Mr. Cadden responded in writing to the 483 detailing a variety of corrective measures. He stated, “We are committed to complying with applicable laws and regulations, to ensuring high-quality care for our patients, and to upgrading our compounding procedures.”⁸⁴ This letter was supplemented on May 16, 2003, detailing additional standard operating procedures that were being implemented at the facility related to compounding, as well as product and environmental testing protocols. Mr. Cadden noted “that while we are validating NECC sterile [injectable] preparation processes, we are not subject to (nor are we voluntarily subjecting ourselves to) current good manufacturing practices (cGMPs) as promulgated by FDA, since we are a compounding pharmacy, not a manufacturer.”⁸⁵

With respect to Massachusetts, the MBP did not commence any regulatory actions until well over a year later, on September 21, 2004, when the Board voted unanimously in favor of proposing a consent agreement to NECC and Mr. Cadden to resolve the aforementioned complaints received and violations observed. Then-Executive Director of the MBP, Charles Young, formally offered Mr. Cadden the consent agreement on October 4, 2004, noting in a letter “that if you choose not to enter into the Agreement, the Board will proceed to a formal hearing.”⁸⁶

According to the terms of the proposed consent agreement, NECC would have to agree that it was entered into “as a result of an adverse event complaint report investigated by the U.S. Food and Drug Administration” alleging that NECC “failed to comply with accepted standards in compounding a certain order for methylprednisolone acetate.”⁸⁷ In addition, NECC would agree that this conduct “constitutes professional misconduct warranting disciplinary action by the Board” and that NECC and Mr. Cadden would be “REPRIMANDED by the Board and [NECC’s] pharmacy registration and [Mr. Cadden’s] pharmacist license [would be] placed on

⁸¹ See U.S. FOOD & DRUG ADMIN., NEW ENGLAND COMPOUNDING CENTER FORM FDA 483 (Feb. 10, 2003) [hereinafter, “FDA FEB. 10, 2003 FORM 483”].

⁸² FDA FEB. 10, 2003 ESTABLISHMENT INSPECTION REPORT, *supra* note 72, at 1.

⁸³ FDA FEB. 10, 2003 INSPECTION REPORT, *supra* note 49, at 20.

⁸⁴ Letter from Barry Cadden, Manager, New England Compounding Center, Inc., to Daryl A. Dewoskin, Investigator, FDA & Kristina M. Joyce, Investigator, FDA (Feb. 26, 2003) [hereinafter, “Feb. 26, 2003 Cadden Letter”].

⁸⁵ Letter from Barry Cadden, Manager, New England Compounding Center, Inc., to Daryl A. Dewoskin, Investigator, FDA & Kristina M. Joyce, Investigator, FDA (May 16, 2003) [hereinafter, “May 16, 2003 Cadden Letter”].

⁸⁶ Letter from Charles R. Young, Executive Dir., Mass. Bd. of Registration in Pharmacy, to Barry J. Cadden, Manager of Record, New England Compounding Ctr. (Oct. 4, 2004) (attaching proposed Consent Agreement).

⁸⁷ Proposed Consent Agreement, *In the Matter of New England Compounding Center Registration No. 2848 Barry J. Cadden, R.Ph. License No. 21239*, Docket Nos. DS-03-055, PH-03-066, at 1 (Mass. Bd. of Registration in Pharmacy, Oct. 4, 2004) [hereinafter, “MPB Proposed Consent Agreement”].

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probation for a minimum three (3) year period.”⁸⁸ During the probationary period, among other things, NECC and Mr. Cadden would have been required to develop and implement various policies and procedures, update the Board on a quarterly basis, and keep written reports of each adverse event reported.⁸⁹ Finally, the agreement would have required NECC and Mr. Cadden to apply in writing for termination of the probationary period, which would be granted only if all the conditions had been met.⁹⁰

On November 11, 2004, counsel for NECC and Mr. Cadden responded to MBP’s offer of the consent agreement. Similar to the company’s prior responses to FDA, the letter, addressed to MBP counsel Susan Manning detailed the various corrective measures that NECC had implemented and noted that they “address –and in some instances exceed – the proposed probationary conditions.”⁹¹ After noting subsequent inspections that had been conducted “without incident,” NECC’s counsel stated, “While I think it is fair to say that the product of NECC’s interaction with the Board . . . is a success story, such would not be the case if the resolution were to include a disciplinary sanction (including the reprimand proposed in Mr. Young’s letter). The collateral consequences to many, if not all of NECC’s 42 other [state] licenses, would be potentially fatal to the business. Such a catastrophe is clearly not the intended result of the Board’s proposed reprimand, nor is it warranted in this case. The Board’s mandate is to protect the public health safety and welfare, not to punish its licensees.”⁹² In conclusion, the attorney stated, “Mr. Cadden and NECC have demonstrated their commitment to remediation, and are prepared to continue to do so. In that regard, NECC and Mr. Cadden will agree to all of the probationary terms offered in Mr. Young’s letter, and will further agree to bear the burden and cost of monitoring and reporting their compliance. That result could be accomplished through a non-disciplinary resolution such as a continuance (pending a period of monitoring) or a ‘stayed probation.’”⁹³ On November 23, 2004, the MBP reviewed the “NECC response to [the] proposed Consent Agreement” and voted unanimously “to deny [the] request to revise terms.”⁹⁴

Despite the October 4, 2004, letter stating that if NECC and Mr. Cadden chose not to enter into the consent agreement, the Board would proceed to a formal hearing, there is no documentation of any such hearing having occurred. However, on January 6, 2006, NECC and Mr. Cadden did sign a consent agreement with MBP, though the terms were significantly different from those proposed by the Board in 2004. As set forth in the next section of this memorandum, NECC and the Massachusetts Board eventually agreed to only a stayed probationary period of one year.

D. 2004 Inspections and the 2006 Massachusetts Board Consent Agreement with NECC

As evidence that MBP was aware of NECC’s corrective measures and disciplinary action was unwarranted, NECC’s counsel pointed out in his November 11, 2004, response letter that

⁸⁸ *Id.* at 1-2.

⁸⁹ *Id.* at 2.

⁹⁰ *Id.*

⁹¹ Letter from Paul R. Cirel, Counsel to Barry Cadden & New England Compounding Ctr., to Susan Manning, Counsel to Mass. Bd. of Registration in Pharmacy, at 1 (Nov. 11, 2004) [hereinafter, “Nov. 11, 2004 Cirel Letter”].

⁹² *Id.* at 2-3 (internal citations omitted).

⁹³ *Id.* at 3 (internal citations omitted).

⁹⁴ Minutes of the Meeting of the Mass. Bd. of Registration in Pharmacy, at 2 (Nov. 23, 2004).

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MBP had “inspected the facility three times since last February (twice, with a representative from the FDA).”⁹⁵ However, the two inspections with FDA were not to follow up on the underlying complaints and violations covered in the proposed consent agreement, but were to investigate new allegations. Further, these inspections revealed additional violations by NECC.

On April 27, 2004, MBP had received a complaint from a Wisconsin pharmacist that raised concerns about the safety and legality of a product NECC was soliciting. According to the complaint, an NECC representative offered “a product to our plastic surgery physician that he calls extra strength triple anesthetic cream.”⁹⁶ During the conversation, NECC “related to [the individual] that he would need a prescription for the product and that we could use the name of a staff member if we wanted to. He said ‘other institutions have used a nurse[‘]s name.’”⁹⁷ When questioned about the legality of this approach, “He assured her it was legal. He indicated that after we received the product it was up to us how we used it and to whom it was administered.”⁹⁸ Separate from this complaint, MBP received “an e-mail sent to the Board by a pharmacist practicing in Iowa. According to the complaint . . . [NECC] is advertising compounded prescription products which may constitute manufacturing since they purport to be used by multiple patients using the same prescription order.”⁹⁹

On September 21, 2004, MBP assigned an investigator to “conduct a joint/inspection with FDA . . . It is alleged that [NECC] is compound[ing] non-FDA product Trypan Blue Dye to be used as a capillary stain during cardiac procedures. This dye is not approved for this use.”¹⁰⁰ On September 23, 2004, investigators from MBP and FDA NWE-DO visited NECC. According to a January 26, 2005, memorandum drafted by the FDA investigator, “This investigation was mainly to obtain information about the firm’s compounding practices, as they relate to the compounding of Trypan blue products.”¹⁰¹ When investigators arrived, Mr. Cadden “acknowledged that he is the most responsible person in the firm” but also introduced them to Gregory Conigliaro who “reported that he just joined the company about eight months ago [and] that he is a Civil Engineer by profession.”¹⁰²

When FDA’s investigator asked Mr. Cadden whether he had Trypan blue in stock, “He said no, because he just compounds the drug if he receives the prescriptions for certain patients.”¹⁰³ However, when the FDA investigator was shown the clean room, he noticed a drawer that was identified as “Trypan Blue.” He requested that Mr. Cadden open the drawer and when he did, the investigator noted that there were 189 vials of the product. After being

⁹⁵ Nov. 11, 2004 Cirel Letter, *supra* note 91, at 2. The letter lists three inspection dates: February 20, 2004, September 23, 2004, and September 28, 2004. The letter further notes that the second and third inspections included a “representative from the FDA.”

⁹⁶ E-mail from Wisconsin Dir. of Pharmacy, to James D. Coffey, Dir., Mass. Bd. of Registration in Pharmacy (Apr. 27, 2004, 11:33 AM).

⁹⁷ *Id.*

⁹⁸ *Id.*

⁹⁹ Mass. Div. of Prof’l Licensure Office of Investigations, *Request for Staff Assignment* (requested May 27, 2004).

¹⁰⁰ Mass. Div. of Prof’l Licensure Office of Investigations, *Request for Staff Assignment* (assigned Sept. 21, 2004).

¹⁰¹ Memorandum from Investigator, New England Dist. Office, FDA, to Acting Team Leader, Div. of New Drugs & Labeling Compliance, FDA, *Inspection/Investigation of New England Compounding Center 697 Waverly Street Framingham, MA 01702*, at 1 (Jan. 26, 2005) [hereinafter, “Jan. 26, 2005 FDA Memorandum”].

¹⁰² *Id.*

¹⁰³ *Id.* at 2.

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informed that it was not an approved product and that NECC should not be compounding it, Mr. Cadden stated that he “did not know that it is not an approved product.”¹⁰⁴ He then “told one of the employees in the laboratory to put the vials in quarantine which he told us will be eventually destroyed.”¹⁰⁵

FDA and MBP investigators returned to NECC on September 28, 2004. When asked about the Trypan blue, Mr. Cadden asserted that his lawyer informed him that he did not have to quarantine the product and that “there is no regulation which states that Compounding Pharmacies cannot compound FDA non-approved drugs.”¹⁰⁶ In addition he informed the investigators that he dispensed the product the day after the last inspection and that he intends to do so “until FDA/MABP will put in writing that they cannot compound it [and] dispense it and the reason why.”¹⁰⁷ When FDA’s investigator asked Mr. Conigliaro additional questions, “he became indignant [and] he said that he does not really have the time to sit with us [and] answer all those questions.”¹⁰⁸ Further, according to the investigator, Mr. Cadden told Mr. Conigliaro, “Don’t answer any more questions!”¹⁰⁹ Prior to leaving, FDA wrote down the questions in the assignment and left them with Mr. Conigliaro. On October 1, 2004, Mr. Conigliaro responded to the questions in writing, which were shared with FDA compliance staff.¹¹⁰

On October 27, 2004, MBP’s investigator sent Mr. Cadden a letter with requests for responses and additional information related to Trypan blue production and distribution, including a fill log and a copy of all prescriptions dispensed “containing more than two (2) doses per patient.”¹¹¹ On November 8, 2004, Mr. Cadden responded to the letter with the requested information, along with corrective actions taken, and stated, “In summary, we regret that the invalid patient names were not discovered by our pharmacy processing staff. We have taken immediate action to insure that physicians provide, and we verify, accurate patient names in the future.”¹¹² This response was shared with FDA’s investigator. On January 19, 2005, the FDA investigator notified Mr. Cadden by phone that the district office was “closing out the inspection based on his response letter to [MBP], indicating his plan of corrective actions, which will also be forwarded to headquarters.”¹¹³

While FDA closed out its inspection, MBP voted on November 23, 2004, to file a formal complaint based on the investigator’s findings.¹¹⁴ This was the same day the Board unanimously voted to deny NECC’s request to revise the terms of the consent agreement that had been proposed on October 4, 2004, covering the complaints and violations associated with

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ *Id.* at 3.

¹⁰⁷ *Id.*

¹⁰⁸ *Id.*

¹⁰⁹ *Id.*

¹¹⁰ *See id.* at 4.

¹¹¹ Letter from Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, to Investigator, Mass. Div. of Health Professions Licensure Office of Investigations, at 2 (Nov. 8, 2004).

¹¹² *Id.*

¹¹³ Jan. 26, 2005 FDA Memorandum, *supra* note 101, at 4.

¹¹⁴ *See* MASS. DEP’T OF PUB. HEALTH, INVESTIGATION REPORT OF BARRY CADDEN, at 2 (Nov. 23, 2004) [hereinafter, “MDPH NOV. 23, 2004 INVESTIGATION REPORT”].

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betamethasone repository injection and methylprednisolone acetate. It is unclear as to whether these decisions were related.

Based on the new terms of the amended consent agreement, the complaint related to distribution of Trypan blue products without valid prescriptions was subsumed into the agreement. Despite the fact that the underlying matters were now more extensive, the amended consent agreement no longer called for a formal reprimand for professional misconduct, a three year probationary period, or a number of mandatory conditions that would have been required prior to the Board terminating the probation. The amended consent agreement included a probationary period of one year that was stayed pending satisfactory documentation related to an inspection having been conducted by Pharmacy Support, Inc. (PSI), a Board-approved evaluator, within 45 days of the effective date of the agreement. Further, NECC had to provide MBP with satisfactory documentation that PSI's recommendations were implemented and that a second inspection was conducted within six months. If such conditions were met, neither NECC's registration nor Mr. Cadden's license would be placed on probation.¹¹⁵

On January 30, 2006, PSI sent its initial audit report to Mr. Cadden and the MBP, noting that the assessment was conducted on January 17 and 18. The cover letter accompanying the report concluded, "Although your facility has seen significant upgrades in facility design for sterile compounding operation, there were numerous significant gaps identified during the assessment therefore, it is the opinion of the auditors that your operation needs to be upgraded and enhanced to be in substantial compliance with United States Pharmacopeia <795> or <797>."¹¹⁶ The letter noted that major areas of concern included the fact that good documentation practices were inadequate; written procedures were admittedly not routinely followed; procedures were not in strict accordance with USP standards; end product testing was often performed on "stock solutions" and not the end product that is required; and validation of sterilization cycles and media fills were inadequate.¹¹⁷ Numerous corrective actions were recommended, including a plan to attain compliance.

On April 7, 2006, PSI issued the final report, which concluded that "[NECC] has made significant improvements over the past several months. They have demonstrated the ability to be compliant with all state and federal regulations. The[y] have appropriate equipment, procedures, basic facility design and environmental controls."¹¹⁸ However, PSI stated that, among other things, "it is the opinion of our firm that in order for NECC to be in substantial compliance . . . [a] [r]edesign of clean room 1 where sterile preparations are compounded (Floor, Ceiling, and HVAC)" must occur.¹¹⁹

¹¹⁵ See Consent Agreement, *In the Matter of New England Compounding Center Registration No. 2848 Barry J. Cadden, R.Ph. License No. 21239*, Docket Nos. DS-03-055, PH-03-066, DS-05-040 (Mass. Bd. of Registration in Pharmacy, Jan. 10, 2006) [hereinafter, "MPB-NECC Consent Agreement"].

¹¹⁶ Letter from Vice President for Quality Operations, Pharm. Systems, Inc., to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center et al., at 2 (Jan. 30, 2006) (attaching initial audit report entitled "Observations Requiring Corrective Action").

¹¹⁷ See *id.* at 1-11.

¹¹⁸ PHARM. SYSTEMS, INC., FINAL REPORT: USP <795>/<797> IMPLEMENTATION – NEW ENGLAND COMPOUNDING CENTER, FRAMINGHAM, MA, at 1 (Apr. 7, 2006) [hereinafter, "PSI Final NECC Report"].

¹¹⁹ *Id.*

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On April 12, 2006, MBP “commend[ed] NECC on the progress to date” and requested that the firm “advise the Board in writing regarding NECC’s intentions” with respect to the outstanding recommendations of PSI as well as “projected timelines for completion.”¹²⁰ Mr. Cadden responded on April 19 as to how NECC would address PSI’s remaining concerns. Regarding the “[r]edesign of clean room 1,” Mr. Cadden stated, “It should first be noted that all sterile preparations are compounded within Class 10 Microenvironments, within ‘clean room 1.’ The room is not maintained as a certified clean room, nor was it ever our intent.”¹²¹ Mr. Cadden did, however, assert that the “HVAC unit in that room will be improved per PSI’s suggestions. The work has been scheduled . . . and is expected to be completed by May 18, 2006.”¹²² On May 10, 2006, MBP requested of NECC written confirmation of HVAC work completion, along with two other items, which Mr. Cadden confirmed on May 22.¹²³ The next day, the Board voted to advise Mr. Cadden that NECC had satisfactorily completed the terms and conditions in the consent agreement. This decision was communicated to Mr. Cadden on June 2, 2006.¹²⁴ Apparently the MBP never shared the PSI report with the FDA.

E. FDA Warning Letter Relating to September 2004 Inspections

Based on violations of the Food, Drug, and Cosmetic Act (FDCA) either observed during FDA’s joint inspections of NECC in September 2004, or otherwise brought to the agency’s attention, FDA issued a Warning Letter to the company on December 4, 2006.¹²⁵ According to FDA’s Regulatory Procedures Manual, “Warning Letters are issued to achieve voluntary compliance and to establish prior notice. . . . The agency position is that Warning Letters are issued only for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected.”¹²⁶

The NECC Warning Letter set forth FDA’s position on the agency’s jurisdiction over new drugs, including compounded drugs, and its enforcement policy with respect to them. The Warning Letter referenced Compliance Policy Guide (CPG), section 460.200 [“Pharmacy Compounding”], which was issued by FDA on May 29, 2002, and several of the factors laid out in the CPG that influence FDA’s enforcement policy in specific cases. The Warning Letter then

¹²⁰ Letter from George A. Cayer, President, Mass. Bd. of Registration in Pharmacy, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (Apr. 12, 2006).

¹²¹ Letter from Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, to George A. Cayer, President, Mass. Bd. of Registration in Pharmacy, at 1 (Apr. 19, 2006).

¹²² *Id.*

¹²³ See Letter from George A. Cayer, President, Mass. Bd. of Registration in Pharmacy, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (May 10, 2006) and Letter from Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, to George A. Cayer, President, Mass. Bd. of Registration in Pharmacy (May 22, 2006).

¹²⁴ See Letter from George A. Cayer, President, Mass. Bd. of Registration in Pharmacy, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (June 2, 2006).

¹²⁵ See Warning Letter (NEW-06-07W) from Gail T. Costello, Dist. Dir., New England Dist. Office, FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (Dec. 4, 2006) [hereinafter, “FDA Warning Letter”].

¹²⁶ U.S. FOOD & DRUG ADMIN., REGULATORY PROCEDURES MANUAL, at § 4-1-1 (2011), available at <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm>.

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discussed four primary areas of NECC activity that constituted violations of the FDCA for which the agency would not exercise its enforcement discretion.¹²⁷

First, FDA noted that NECC may be compounding copies of commercially available drug products. Specifically, FDA highlighted Trypan blue products and the fact that “on December 16, 2006, trypan blue ophthalmic solution was approved by FDA and it is commercially available.”¹²⁸ In addition, according to the Warning Letter, FDA also learned that NECC “may be compounding 20% aminolevulinic acid solution,” another commercially available, FDA-approved product.¹²⁹ FDA informed NECC that “FDA does not sanction the compounding of copies of FDA-approved, commercially available drugs and the agency will not exercise its enforcement discretion regarding the trypan blue and ALA products compounded by your firm.”¹³⁰

Second, FDA detailed how NECC had developed a standardized anesthetic drug product, promoted and sold it under the name “Extra Strength Triple Anesthetic Cream,” and generated sales by giving physicians free samples. In addition to noting the public health risks associated with high dose local anesthetic creams, FDA stated, “These actions are not consistent with the traditional practice of pharmacy compounding, in which pharmacists extemporaneously compound reasonable quantities of drugs upon receipt of valid prescriptions from licensed practitioners to meet the unique medical needs of individual patients.”¹³¹

Third, FDA informed Mr. Cadden that it was “in receipt of a complaint alleging that [NECC was] repackaging the approved injectable drug, Avastin, into syringes for subsequent promotion and sale to health professionals.”¹³² The Warning Letter explained that FDA has an established policy, articulated in the CPG, concerning the manipulation of approved sterile drug products outside the scope of FDA approval and that FDA was “especially concerned with the potential microbial contamination associated with splitting Avastin – a single-use, preservative-free, vial – into multiple doses.”¹³³

Finally, FDA stated that the agency had been informed that “although [NECC] advises physicians that a prescription for an individually identified patient is necessary to receive compounded drugs, [the] firm has reportedly also told physicians’ offices that using a staff member’s name on the prescription would suffice.”¹³⁴

FDA concluded the Warning Letter by informing Mr. Cadden that “[f]ailure to promptly correct these deviations may result in additional regulatory action without further notice, including seizure or injunction against you and your firm.”¹³⁵ The agency asked to be notified in

¹²⁷ See FDA Warning Letter, *supra* note 125, at 2-5.

¹²⁸ *Id.* at 2.

¹²⁹ *Id.*

¹³⁰ *Id.* at 2-3.

¹³¹ *Id.* at 3.

¹³² *Id.* at 4.

¹³³ *Id.*

¹³⁴ *Id.* at 5.

¹³⁵ *Id.*

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writing of “any steps that you will take to correct the noted violations, including an explanation of the steps taken to prevent the recurrence of similar violations.”¹³⁶

On January 5, 2007, Mr. Cadden responded to FDA by noting at the outset that “the Warning Letter is based on an inspection of NECC that started on September 23, 2004, approximately twenty-eight months ago . . . FDA has not contacted us since concluding the inspection. Some of the letter’s assertions no longer apply to NECC’s operations.”¹³⁷ After disputing FDA’s claim to having jurisdiction over compounded drugs, Mr. Cadden stated that “NECC does not compound copies of FDA-approved commercially available drugs, introduce unapproved new drugs into interstate commerce, does not need approved [New Drug Applications] before dispensing its compounded medications, and does not process or repackage approved drugs in a manner that would subject us to FDA regulation. Nor are our compounded medications misbranded. NECC dispenses compounded medications upon the receipt of valid prescriptions.”¹³⁸

Without agreeing with the Warning Letter’s assertions, Mr. Cadden informed FDA that, for business reasons, NECC stopped filling prescriptions for Trypan blue in August 2005 (sixteen months before the Warning Letter) and for 20% aminolevulinic acid solution in May 2006 (seven months before the Warning Letter).¹³⁹

With respect to the topical anesthetic cream, Mr. Cadden asserted that NECC currently used the term “‘triple anesthetic cream’ . . . but only as a way to literally describe the compounded medication as a convenience to our prescribing physicians. The term is in no way trademarked or branded.”¹⁴⁰ Further, Mr. Cadden noted, “Although we do provide a very small quantity of medications (less than ten per month) free of charge, we do so only upon receipt of a valid prescription from a licensed practitioner to meet the unique medical needs of a particular patient. . . . A valid prescription does not become unlawful just because we do not charge the physician or patient. Should the FDA believe our position on this matter is incorrect, please advise.”¹⁴¹

Regarding the repackaging of Avastin, Mr. Cadden stated that it did not constitute manufacturing, that NECC only did so “upon receipt of a valid, patient-specific prescription,” and that “[a]ll aspects of our sterile compounding and repacking operations were recently reviewed by an independent expert, who confirmed that NECC is in compliance with [USP standards].”¹⁴²

Lastly, in response to FDA’s assertion that NECC reportedly told physicians that the company would fill prescription written in the name of a staff member, Mr. Cadden stated, “This

¹³⁶ *Id.*

¹³⁷ Letter from Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, to Compliance Officer, New England Dist. Office, FDA et al., at 1 (Jan. 5, 2007).

¹³⁸ *Id.* at 3.

¹³⁹ *See id.* at 3.

¹⁴⁰ *Id.* at 4.

¹⁴¹ *Id.* at 4-5.

¹⁴² *Id.* at 5.

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allegation contradicts all of our standard operating procedures. NECC has not made such a representation to anyone, and has no idea how or why FDA arrived at this allegation.”¹⁴³

FDA did not respond to Mr. Cadden’s letter until almost two years later, on October 31, 2008. In its reply, the agency “acknowledge[d] and apologize[d] for the significant delay in this correspondence.”¹⁴⁴ Again, FDA presented an extensive summary of its authority over compounded drugs and factors the agency would consider in determining whether to exercise enforcement discretion. FDA accepted the firm’s assertions with respect to the discontinued products; however, NECC’s letter did not alleviate FDA’s concerns regarding the manner in which the company was promoting its products and the manipulation of sterile injectables.¹⁴⁵

FDA concluded by stating, “We agree that the length of intervening period was unusual. This in no way diminishes our serious concerns about your firm’s operation. Your firm must promptly correct the violations noted in the December 4, 2006, Warning Letter, and establish procedures to assure that such violations do not occur. Its failure to do so may result in enforcement action including seizure of the firm’s products and/or an injunction against the firm and its principals. In a future inspection, we will confirm the commitments that you made in your response. We also will verify that your firm’s compounding practices are consistent with the policy articulated in the CPG, and that your firm’s operation is not otherwise at odds with the conditions under which the agency exercises enforcement discretion towards pharmacy compounding.”¹⁴⁶ This letter, which was dated October 31, 2008 and sent in follow-up to an inspection that occurred in September 2004, is the last documented correspondence between FDA and NECC until the recent outbreak.

F. Recent Colorado Complaints Related to NECC and Corresponding Actions

With respect to additional correspondence between NECC and State authorities, the next interaction between the parties was a satisfactory MBP inspection conducted on May 24, 2011, in connection with the renovation and expansion of NECC’s Framingham facility. This was the last inspection of NECC’s facility prior to the meningitis outbreak.

On July 26, 2012, however, an inspector for the Colorado Board of Pharmacy notified MBP Director James Coffey that NECC had violated the terms of a Cease and Desist Order the State had issued the company on April 15, 2011, based on NECC’s distribution of “a stock compounded prescription drug . . . to a prescription drug outlet in the State of Colorado.”¹⁴⁷ Mr. Coffey was informed that, during the course of a routine hospital pharmacy inspection in Colorado on July 17, 2012, the inspector observed a number of invoices and products from NECC. After this conversation, on July 26, 2012, the Colorado inspector emailed Mr. Coffey a copy of “the Special Report submitted to the Chief Inspector for the Pharmacy Board in

¹⁴³ *Id.* at 6.

¹⁴⁴ Letter from Compliance Officer, New England Dist. Office, FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center, at 1 (Oct. 31, 2008).

¹⁴⁵ *See id.* at 2-4.

¹⁴⁶ *Id.* at 4.

¹⁴⁷ *See* Cease and Desist Order, *In the Matter of the Unauthorized and Unlawful Distribution of Prescription Drugs and/or Compounded Prescription Drugs in Colorado by New England Compounding Center, Inc.*, Case No. 2011-3973 (Colo. State Bd. of Pharmacy, Apr. 15, 2011).

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Colorado concerning the receipt of non-patient specific compounded products into Colorado.”¹⁴⁸ The inspector asked Mr. Coffey for “any information that the Massachusetts Board could provide concerning if this practice is allowed under Massachusetts pharmacy law.”¹⁴⁹ Mr. Coffey responded on July 27, “The Massachusetts Board of Pharmacy will respond as soon as possible following a thorough review and analysis of the same.”¹⁵⁰ Mr. Coffey then forwarded his correspondence with the Colorado inspector, along with the report, to MBP counsel Susan Manning and others in the MDPH, including several past NECC inspectors.¹⁵¹

Included in the Colorado report is email correspondence from May 2011 between FDA’s Denver and New England District Offices relating to NECC’s “illegal distribution of compounded drugs to hospitals in the Denver metropolitan area.”¹⁵² Several FDA employees were on this email chain, including at least one NWE-DO compliance officer involved in past NECC actions. Based on the Committee’s investigation, it appears that FDA did not contact the MBP about the Colorado Board’s concerns in May 2011 or any time thereafter, as Mr. Coffey was first informed by the Colorado inspector on July 26, 2012.

MDPH officials informed Committee staff that they first became aware of this complaint from Colorado while reviewing responsive documents pursuant to the Committee’s investigation. On November 6, 2012, Dr. Lauren Smith, MDPH Interim Commissioner, issued a statement that Mr. Coffey had been terminated and Susan Manning had been placed on administrative leave. According to Dr. Smith, “The director of the Board is responsible for ordering investigations. Mr. Coffey failed to order an investigation or take any other action on the Colorado complaint. It is incomprehensible that Mr. Coffey and Ms. Manning did not act on the Colorado complaint given NECC’s past, and their responsibility to investigate complaints. Following the outbreak, staff also failed to disclose the existence of Colorado’s complaint to leadership at DPH.”¹⁵³ Dr. Smith stated that “[t]here is no evidence at this time that staff informed Board [of Pharmacy] members about the Colorado issues. We continue to interview all Board members as part of our investigation into their handling of this situation and will not hesitate to make further changes and personnel actions if we deem them to be necessary.”¹⁵⁴ However, it has come to the Committee’s attention that as of November 8, 2012, the current President of the Board has yet to be interviewed.

¹⁴⁸ E-mail from Pharmacy Inspector, Colo. State Bd. of Pharmacy, to James D. Coffey, Dir., Mass. Bd. of Registration in Pharmacy (July 26, 2012, 3:06 PM).

¹⁴⁹ *Id.*

¹⁵⁰ E-mail from James D. Coffey, Dir., Mass. Bd. of Registration in Pharmacy, to Pharmacy Inspector, Colo. State Bd. of Pharmacy (July 27, 2012, 7:33 AM).

¹⁵¹ See E-mail from James D. Coffey, Dir., Mass. Bd. of Registration in Pharmacy, to Susan Manning, Counsel to Mass. Bd. of Registration in Pharmacy et al. (July 27, 2012, 7:34 AM) (forwarding Colorado “Special Report”).

¹⁵² E-mail from Senior Case Review Expert, Denver Dist. Office, FDA, to Supervising Consumer Safety Officer, New England Dist. Office, FDA et al. (May 10, 2011, 4:19 PM).

¹⁵³ Press Release, Mass. Dep’t of Pub. Health, Statement of Interim Commissioner Dr. Lauren Smith on NECC Investigation (Nov. 7, 2012), *available at* http://www.mass.gov/eohhs/docs/dph/quality/boards/pharmacy/12110_7-statement-from-lauren-smith.pdf.

¹⁵⁴ *Id.*

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IV. ISSUES

The following issues will be explored at the hearing:

- Both State and Federal inspectors documented a number of deficiencies and violations at NECC since as early as 2002, many of which are similar to those at issue in the ongoing meningitis investigation. Were the FDA's and the Massachusetts Board of Pharmacy's enforcement actions appropriate?
- Why didn't FDA pursue any enforcement actions against the NECC despite having emphasized in 2003 the potential for serious public health consequences if the company's compounding practices, in particular those relating to sterile products, were not improved?
- Prior to this outbreak, the Massachusetts Board of Pharmacy had investigated at least twelve separate complaints relating to NECC and its management. While many of these complaints covered NECC's sales and marketing tactics, several were associated with serious adverse events and uncovered deficiencies with NECC's compounding operations. How was NECC able to maintain its pharmacy license despite repeated violations?
- What did State and Federal authorities do to confirm that sufficient corrective measures were taken after these inspections? How did they communicate with each other to ensure such responses were adequate to protect the public health?

V. STAFF CONTACTS

If you have any questions regarding this hearing, please contact Karen Christian or John Stone with the Subcommittee on Oversight and Investigations at (202) 225-2927.